obvious typographical errors. A substitute Sequence Listing and a substitute computer readable form (CRF) copy of the Sequence Listing are provided. No new matter has been introduced.

The substitute Sequence Listing has fewer sequences than the previous Sequence Listing it replaces, despite incorporation in the substitute Sequence Listing of the sequence in Claims 11, 40, 49, 62, and 68. This reduced number of sequences is the result of elimination of (a) sequences not meeting the requirements for inclusion in the Sequence Listing, (b) sequences appearing more than once in the previous Sequence Listing, and (c) sequences appearing in the previous Sequence Listing without apparent corresponding sequence appearing elsewhere in the specification. The following SEQ ID NOs according to the previous Sequence Listing have thus been eliminated: 26-34, 36, 37, 39, 41, 44, 50, 51, 75, and 106-110. In this manner, SEQ ID NO:26 in the substitute Sequence Listing corresponds to SEQ ID NO:35 in the previous Sequence Listing, SEQ ID NO:27 in the substitute Sequence Listing corresponds to SEQ ID NO:38 in the previous Sequence Listing, and so on. The sequence in Claims 11, 40, 49, 62, and 68 is incorporated in the substitute Sequence Listing as SEQ ID NO:89.

The specification is amended in accord with the substitute Sequence Listing. SEQ ID NOs in the specification have been amended to associate each unique sequence therein with a unique SEQ ID NO. This includes identifying with a SEQ ID NO sequences appearing in the paragraph beginning at line 17 on page 6; the paragraph beginning at line 30 on page 12; the paragraph at lines 18-27 on page 36; and the paragraph beginning at line 16 on page 51. Except for the sequence in Claims 11, 40, 49, 62, and 68 identified in the substitute Sequence Listing as SEQ ID NO:89, these sequences were included and assigned SEQ ID NOs in the previous Sequence Listing. Certain sequences occurring in the paragraph beginning at line 7 on page 39 have been eliminated due to inadvertent duplication. The SEQ ID NO identifiers in Tables 1-7 have been amended to associate each unique sequence therein with a unique SEQ ID NO and to eliminate SEQ ID NOs for each sequence not requiring a SEQ ID NO.

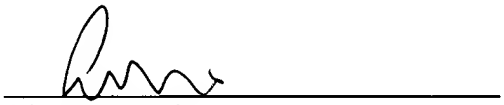
The specification is also amended to correct certain obvious typographical errors. In particular, the term "CpG-DON" has been corrected to read "CpG-ODN" in paragraphs found on pages 56 and 57.

Claims 11, 40, 49, 62, and 68 have been amended as required by the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid

Sequence Disclosures. Applicants assert that the amendments to the affected claims are to be entered solely to satisfy this formality and not for reasons of patentability.

It is believed that the application as amended is now in conformity with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures, and that the claims are in condition for allowance. Favorable action is earnestly solicited. If for any reason the examiner has any question or would require further information, she is encouraged to contact the Applicant's representative at the number presented below.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| Applicant: | Wagner et al. |
| Serial No: | 09/241,653 |
| Filed: | February 2, 1999 |
| For: | METHODS FOR REGULATING HEMATOPOIESIS USING CpG-OLIGONUCLEOTIDES |
| Examiner: | J. Zara |
| Art Unit: | 1635 |



**CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)**

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to Commissioner for Patents, Washington, D.C. 20231, on the 12th day of October, 2001.

Alan W. Steele

Commissioner for Patents
Washington, D.C. 20231

## Appendix

The following are marked-up versions of paragraphs, tables, and claims amended in response to the Office Action dated September 12, 2001.

## In the Specification

(1) On page 6-7, the paragraph beginning at line 17 on page 6 (amended):

Cytokine production and hematopoiesis

As described above the cytokine repertoire induced by CpG-ODN injection is Th1 in nature, and ample evidence suggests this exerts a strong Th1 biasing effect to the subsequent immune response development. Zhao et al. administered to mice a 27-mer phosphorothioate oligonucleotide (sequence 5'-TCG TCG CTG TCT CCG CTT CTT CTT GCC-3'; SEQ ID NO:54), which had previously been shown to cause splenomegaly and hypergammaglobulinemia upon *in vivo* administration in mice, and studied the pattern and kinetics of cytokine production at both the splenic mRNA and serum protein levels. Zhao et al. (1997) Antisense Nucleic Acid Drug Dev 7:495-502. Following i.p. administration of 50 mg/kg of oligonucleotide, significant

increases in the splenic mRNA levels of IL-6, IL-12 p40, IL-1β, and IL-1Ra and serum levels of IL-6, IL-12, MIP-1β, and MCP-1 were observed. In contrast, no significant differences in splenic mRNA levels of IL-2, IL- 4, IL-5, IL-9, IL-13, IL-15, IFN-γ, or MIF or serum levels of IL-2, IL-4, IL-5, IL-10, IFN-γ, or GM-CSF were detected. These studies show a distinct pattern and kinetics of cytokine production following oligonucleotide administration and further demonstrate that cytokine induction is not a general property of phosphorothioate oligonucleotides but is dependent on the sequence and dose of the oligonucleotides. Serum release of IL-1, IL-6, IL-12 and TNF-α was also confirmed by Lipford et al. Lipford, GB et al. (1997) Eur J Immunol 27:2340-2344.

(2) On pages 12-13, the paragraph beginning at line 30 on page 12 (amended):

In another embodiment the CpG oligonucleotide has a sequence including at least the following formula:

5' TCNTX$_1$X$_2$CGX$_3$X$_4$ 3' (SEQ ID NO:89)

wherein X$_1$, X$_2$[,], X$_3$[,], and X$_4$ are nucleotides, and N is a nucleic acid sequence composed of from 0-25 nucleotides.

(3) On page 36, the paragraph at lines 18-27 (amended):

In another embodiment the invention provides an isolated CpG oligonucleotide represented by the formula:

5'_N$_1$X$_1$X$_2$CGX$_3$X$_4$N$_2$_3'

wherein at least one nucleotide separates consecutive CpGs; X$_1$X$_2$ is selected from the group consisting of TpT, CpT, TpC, and ApT; X$_3$X$_4$ is selected from the group consisting of GpT, GpA, ApA and ApT; N is any nucleotide and N$_1$ and N$_2$ are nucleic acid sequences composed of from about 0-25 N's. In a preferred embodiment N$_1$ and N$_2$ of the nucleic acid do not contain a CCGG quadmer or more than one CCG or CGG trimer. In another preferred embodiment the CpG oligonucleotide has the sequence 5'_TCN$_1$TX$_1$X$_2$CGX$_3$X$_4$_3' (SEQ ID NO: 89).

(4) On page 39, the paragraph beginning at line 7 (twice amended):

The nucleic acid sequences of the invention which are useful for inducing immune remodeling are those broadly described above. Exemplary sequences include but are not limited to those sequences shown in Table 1-7 as well as TCCATGTCGCTCCTGATGCT (SEQ ID NO:[ 49]35), TCCATGTCGTTCCTGATGCT (SEQ ID NO:[ 59]43), [TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID NO: 97), ]TCGTCGTTGTCGTTGTCGTT (SEQ ID NO:[ 96]79); TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID NO:[ 97]80), TCGTCGTTGTCGTTTTGTCGTT (SEQ ID NO:[ 98]81), GCGTGCGTTGTCGTTGTCGTT (SEQ ID NO:[ 99]82), TGTCGTTTGTCGTTTGTCGTT (SEQ ID NO:[ 101]84), TGTCGTTGTCGTTGTCGTT (SEQ ID NO:[ 103]86), TCGTCGTCGTCGTT (SEQ ID NO:[ 104]87), TCCTGTCGTTCCTTGTCGTT (SEQ ID NO:[ 85]68), TCCTGTCGTTTTTTGTCGTT (SEQ ID NO:[ 87]70), TCGTCGCTGTCTGCCCTTCTT (SEQ ID NO:[ 89]72), TCGTCGCTGTTGTCGTTTCTT (SEQ ID NO:[ 90]73), [TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID NO: 97), TCGTCGTTGTCGTTTTGTCGTT (SEQ ID NO: 98) TGTCGTTGTCGTTGTCGTT (SEQ ID NO: 103), ] TCCATGACGTTCCTGACGTT (SEQ ID NO:[ 88]71), GTCG(T/C)T and TGTCG(T/C)T.

(5) On Page 51, the paragraph beginning at line 16 (amended):

***Microbial stimuli and synthetic oligonucleotides.*** Phosphorothioate-stabilized oligonucleotides (ODN) were synthesized by TibMolBiol (Berlin, Germany). ODN sequences 'CG1' (= ODN 1668, containing a 'CG-motif' marked with bold letters: 5'-TCC-AT**G-ACG-TT**C-CTG-ATG-CT; SEQ ID NO:24) and control GC-ODN ('inverted CG' = ODN 1720: 5'-TCC-AT**G-AGC-TT**C-CTG-ATG-CT; SEQ ID NO:29) were taken from Krieg, AM et al. (1995) Nature 374:546-549. A second CpG-ODN 'CG2' (= ODN IL12p40: 5'-AGC-TAT-**GAC-GTT**-CCA-AGG; SEQ ID NO:30) and control ODN 'nCG' ('non-CG' = ODN AP1, without CG-motif: 5'-GCT-TGA-TGA-CTC-AGC-CGG-AA; SEQ ID NO:65) were described recently. Lipford, GB et al. (1997) Eur J Immunol 27:2340-2344. LPS from *E. coli* was purchased from Sigma (Munich, Germany). *Listeria monocytogenes* came from ATCC (American type culture collection strain 43251) and were grown in brain hear infusion (Difco,

Detroit, USA) in overnight cultures. Number of bacteria was determined by $OD_{600}$ and checked by plating 10 µl aliquots of a serial 10-fold dilution on Columbia blood agar plates and counting the colony forming units after overnight incubation at 37°C.

Please refer to subsequent sheets for items (6) – (12) pertaining to Tables 1-7 (amended).

(13) On page 56, the paragraph beginning at line 4 (amended):

The induction of splenic hematopoiesis was CpG-[DON]ODN dose and sequence dependent (Fig. 4, also see Fig. 3D, table 1b and 1c). Sequences lacking the 'CpG-motif' (nCG) failed to induce extramedullary hematopoiesis and CG inversion (GC-ODN) almost completely abolished the hematopoietic effect of the ODN CG1. Single shot injection of CpG ODN also compared well with the documented hematopoietic activity triggered by LPS (Fig. 4). Apte, RN et al. (1976) J Cell Physiol 71-78; Apte, RN et al. (1976) Exp Hematol 4:10-18; Staber, FG et al. (1980) Proc Natl Acad Sci USA 77:4322-4325. In addition to the granulocyte-macrophage progenitors, the number of pure erythroid progenitors post CpG ODN injection was also increased as determined by the number of Burst-forming Units (BFU-E) per spleen (Fig. 5). Analysis of peripheral blood over 12 days revealed no significant changes apart from a transient leukocytosis at day 2-4. Thus the transient splenomegaly observed in ssDNA injected mice was CpG motif dependent and associated with extramedullary hematopoiesis.

(14) On page 57, the paragraph beginning at line 14 (amended):

***CpG-ODN mediate radioprotective effects in myelosuppression.*** Hematopoietic progenitor cells are considered as rather radioresistant. Morrison, SJ et al. (1995) Annu Rev Cell Dev Biol 11:35-71. Since CpG-[DON]ODN induce extramedullary hematopoiesis via mobilization of CFU-S to the spleen we analyzed whether CpG-ODN could mediate radioprotective effects in sublethally irradiated mice. CpG challenge of sublethally irradiated mice (4 Gy) lead [within day s to a 4 fold increase] within 14 days to a 4 fold increase of splenic GM-CFU (Fig. 7A). Next, we addressed the question whether CpG-ODN driven hematopoiesis

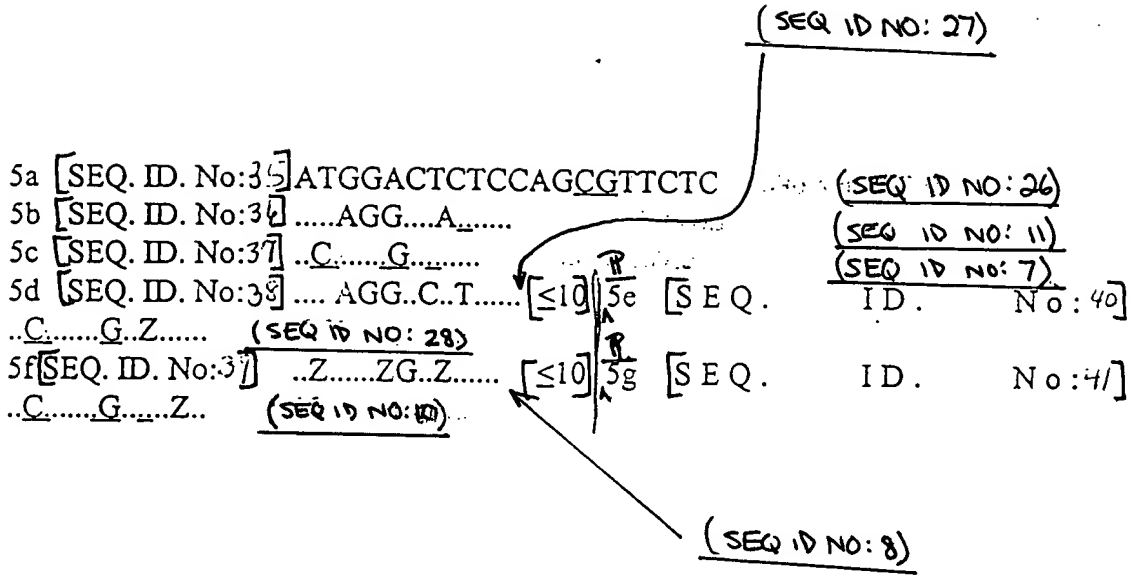
in sublethally irradiated mice allows accelerated recovery of the immune system. Two experimental systems were chosen: one, the induction of CTL responses to proteinaceous antigens (Lipford, GB et al. (1997) Eur J Immunol 27:2340-2344), and two, resistance to the intracellular pathogen *Listeria monocytogenes* (Endres, R et al. (1997) Immunity 7:419-432). Mice were treated with CpG-ODN within 30 minutes after sublethal irradiation (4 Gy), allowed to recover for 18 days and thereafter immunized subcutaneously (s.c.) with ovalbumin (OVA) containing liposomes plus QuilA as adjuvant. After 4 days cells of draining lymph nodes were harvested, cultured for an additional four days and assayed for OVA specific CTL activity. As detailed in Fig. 7B lymphocytes from CpG-ODN treated irradiated mice displayed an enhanced CTL response compared to non-treated irradiated mice. Basically similar results were obtained in an infection model using *L.* [*M*]*monocytogenes* infection at day 14. Overall the data given in Fig. 7 demonstrate a correlation between CpG-ODN induced extramedullary hematopoiesis and the ability to mount cytotoxic T cell responses or protective immune responses towards bacterial infections. CpG-ODN compensate radiation induced damage of the lympho-hematopoietic system by accelerating regeneration from hematopoietic progenitor cells.


**Table 1**

| ODN | Sequence (5' [to] 3') [t] | SEQ ID NO: |
|---|---|---|
| 1 [(SEQ ID NO: 1)] | GCTAGACGTTAGCGT | 1 |
| 1a [(SEQ. ID NO:2)] | ......T.....__. | 2 |
| 1b [(SEQ ID NO: 3)] | ......Z.....__. | 3 |
| 1c [(SEQ ID NO: 4)] | ......__....Z.. | 4 |
| 1d [(SEQ ID NO: 5)] | ..AT..__..GAGC. | 5 |
| 2 [(SEQ ID NO: 6)] | ATGGAAGGTCCAGCGTTCTC | 6 |
| 2a [(SEQ ID NO: 7)] | ..C..CTC..G..__..... | 7 |
| 2b [(SEQ ID NO: 8)] | ..Z..CTC.ZG..Z..... | 8 |
| 2c [(SEQ ID NO: 9)] | ..Z..CTC..G..__..... | 9 |
| 2d [(SEQ ID NO: 10)] | ..C..CTC..G..__..Z.. | 10 |
| 2e [(SEQ ID NO: 11)] | ............A__..... | 11 |
| 3D [(SEQ ID NO. 12)] | GAGAACGCTGGACCTTCCAT | 12 |
| 3Da[(SEQ ID NO: 13)] | .....__..C..... | 13 |
| 3Db[(SEQ ID NO: 14)] | .....__..C.....G.. | 14 |
| 3Dc[(SEQ ID NO: 15)] | ...C.A.............. | 15 |
| 3Dd[(SEQ ID NO: 16)] | .....Z.............. | 16 |
| 3De[(SEQ ID NO: 17)] | .....__.....Z..... | 17 |
| 3Df[(SEQ ID NO: 18)] | .....__A........... | 18 |
| 3Dg[(SEQ ID NO: 19)] | .....__..CC.G.ACTG.. | 19 |
| 3M [(SEQ ID NO: 20)] | TCCATGTCGGTCCTGATGCT | 20 |
| 3Ma[(SEQ ID NO: 21)] | ......CT........... | 21 |
| 3Mb[(SEQ ID NO: 22)] | .......Z........... | 22 |
| 3Mc[(SEQ ID NO: 23)] | .....__..Z........ | 23 |
| 3Md[(SEQ ID NO: 24)] | ......A__T......... | 24 |
| 3Me[(SEQ ID NO: 25)] | .....__.....C..A. | 25 |
| 4 [(SEQ ID NO. 26)] | TCAACGTT | |
| 4a[..... 27)] | ....GC.. | |
| 4b[..... 28)] | ...GCGC. | |
| 4c[..... 29)] | ...TCGA. | |
| 4d[..... 30)] | ..TT__AA | |
| 4e[..... 31)] | -...__.. | |
| 4f[..... 32)] | C...__.. | |
| 4g[..... 33)] | --..__..CT | |
| 4h[..... 34)] | ....__.C | |

-66-

**Table 2**




5'GCATGACGTTGAGCT3' (SEQ. ID. No:[42]5)
5'GCTAGATGTTAGCGT3' (SEQ. ID. No:[43]2)

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**Table 3**

| | |
|---|---|
| 512<br>SEQ ID NO:[14]29 | TCCATGTCGGTCCTGATGCT |
| 1637<br>SEQ ID NO:[15]31 | .....C..... |
| 1615<br>SEQ ID NO:[16]32 | .....G..... |
| 1614<br>SEQ ID NO:[17]33 | .....A..... |
| 1636<br>SEQ ID NO:[18]34 | .....A..... |
| 1634<br>SEQ ID NO [19]35 | .....C..... |
| 1619<br>SEQ ID NO:[50]43 | .....T..... |
| 1618<br>SEQ ID NO:[51]24 | .....A..T..... |
| 1639<br>SEQ ID NO:[52]36 | .....AA..T..... |
| 1707<br>SEQ ID NO:[53]37 | .....A..TC..... |
| 1708<br>SEQ ID NO:[54]38 | .....CA..TG..... |

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**Table 4**

| | |
|---|---|
| 1585 ggGGTCAACGTTGACgggg | (SEQ ID [No 55] NO: 39) |
| 1629 ----------gtc---------- | (SEQ ID [No. 56] NO: 40) |
| 1613 GCTAGACGTTAGTGT | (SEQ ID [No. 57] NO: 41) |
| 1769 ----------Z---------- | (SEQ ID [No 58] NO: 42) |
| 1619 TCCATGTCGTTCCTGATGCT | (SEQ ID [No 59] NO: 43) |
| 1765 ----------Z---------- | (SEQ ID [No. 60] NO: 44) |

-69-

**Table 5**

| ODN | Sequence [5'-3'] (5'→3') | SEQ ID [NO:] NO: |
|---|---|---|
| 1754 | ACCATGGACGATCTGTTTCCCCTC | [61] 45 |
| 1758 | TCTCCCAGCGTGCGCCAT | [62] 46 |
| 1761 | TACCGCGTGCGACCCTCT | [63] 47 |
| 1776 | ACCATGGACGAACTGTTTCCCCTC | [64] 48 |
| 1777 | ACCATGGACGAGCTGTTTCCCCTC | [65] 49 |
| 1778 | ACCATGGACGACCTGTTTCCCCTC | [66] 50 |
| 1779 | ACCATGGACGTACTGTTTCCCCTC | [67] 51 |
| 1780 | ACCATGGACGGTCTGTTTCCCCTC | [68] 52 |
| 1781 | ACCATGGACGTTCTGTTTCCCCTC | [69] 53 |
| 1823 | GCATGACGTTGAGCT | [70] 5 |
| 1824 | CACGTTGAGGGGCAT | [71] 55 |
| 1825 | CTGCTGAGACTGGAG | [72] 56 |
| 1828 | TCAGCGTGCGCC | [73] 57 |
| 1829 | ATGACGTTCCTGACGTT | [74] 58 |
| 1830[2] | RANDOM SEQUENCE | [75] |
| 1834 | TCTCCCAGCGGGCGCAT | [76] 59 |
| 1836 | TCTCCCAGCGCGCGCCAT | [77] 60 |
| 1840 | TCCATGTCGTTCCTGTCGTT | [78] 61 |
| 1841 | TCCATAGCGTTCCTAGCGTT | [79] 62 |
| 1842 | TCGTCGCTGTCTCCGCTTCTT | [85] 63 |
| 1851 | TCCTGACGTTCCTGACGTT | [87] 64 |

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-70-

Table 6

| ODN[1] | Sequence [(5'-3')] (5'→3') | | SEQ ID NO: |
|---|---|---|---|
| 1840 | TCCATGTCGTTCCTGTCGTT | [82] | 61 |
| 1960 | TCCTGTCGTTCCTGTCGTT | [83] | 66 |
| 1961 | TCCATGTCGTTTTTGTCGTT | [84] | 67 |
| 1962 | TCCTGTCGTTCCTTGTCGTT | [85] | 68 |
| 1963 | TCCTTGTCGTTCCTGTCGTT | [86] | 69 |
| 1965 | TCCTGTCGTTTTTTGTCGTT | [87] | 70 |
| 1966 | TCGTCGCTGTCTCCGCTTCTT | [88] | 63 |
| 1967 | TCGTCGCTGTCTGCCCTTCTT | [89] | 72 |
| 1968 | TCGTCGCTGTTGTCGTTTCTT | [90] | 73 |
| 1979[2] | TCCATGTZGTTCCTGTZGTT | [91] | 74 |
| 1982 | TCCAGGACTTCTCTCAGGTT | [92] | 75 |
| 1990 | TCCATGCGTGCGTGCGTTTT | [93] | 76 |
| 1991 | TCCATGCGTTGCGTTGCGTT | [94] | 77 |
| 2002 | TCCACGACGTTTTCGACGTT | [95] | 78 |
| 2005 | TCGTCGTTGTCGTTGTCGTT | [96] | 79 |
| 2006 | TCGTCGTTTTGTCGTTTTGTCGTT | [97] | 80 |
| 2007 | TCGTCGTTGTCGTTTTGTCGTT | [98] | 81 |
| 2008 | GCGTGCGTTGTCGTTGTCGTT | [99] | 82 |
| 2010 | GCGGCGGGCGGCGCGCGCCC | [100] | 83 |
| 2012 | TGTCGTTTGTCGTTTGTCGTT | [101] | 84 |
| 2013 | TGTCGTTGTCGTTGTCGTTGTCGTT | [102] | 85 |
| 2014 | TGTCGTTGTCGTTGTCGTT | [103] | 86 |
| 2015 | TCGTCGTCGTCGTT | [104] | 87 |
| 2016 | TGTCGTTGTCGTT | [105] | 88 |
| 1841 | TCCATAGCGTTCCTAGCGTT | [106] | 62 |

**Table 7**

| ODN[1] | Sequence[5'-3'](5'→3') | SEQ ID NO: |
|---|---|---|
| 1962 | TCCTGTCGTTCCTTGTCGTT [107] | 68 |
| 1965 | TCCTGTCGTTTTTTGTCGTT [108] | 70 |
| 1967 | TCGTCGCTGTCTGCCCTTCTT [109] | 72 |
| 1968 | TCGTCGCTGTTGTCGTTTCTT [110] | 73 |
| 2005 | TCGTCGTTGTCGTTGTCGTT [111] | 79 |
| 2006 | TCGTCGTTTTGTCGTTTTGTCGTT [112] | 80 |
| 2014 | TGTCGTTGTCGTTGTCGTT [113] | 86 |
| 2015 | TCGTCGTCGTCGTT [114] | 87 |
| 2016 | TGTCGTTGTCGTT [115] | 88 |
| 1668 | TCCATGACGTTCCTGATGCT[SEQ.ID.NO:116] | 24 |
| 1758 | TCTCCCAGCGTGCGCCAT[SEQ.ID.NO:117] | 46 |

**In the Claims**

11. (Twice Amended) The method of claim 1, wherein the CpG oligonucleotide has a sequence including at least the following formula:

5' $TCNTX_1X_2CGX_3X_4$ 3' (SEQ ID NO:89)

wherein $X_1$, $X_2$, $X_3$, and $X_4$ are nucleotides, N is a nucleic acid sequence composed of from about 0-25 nucleotides.

40. (Twice Amended) The method of claim 27, wherein the CpG oligonucleotide has a sequence including at least the following formula:

5' $TCNTX_1X_2CGX_3X_4$ 3' (SEQ ID NO:89)

wherein $X_1$, $X_2$, $X_3$, and $X_4$ are nucleotides, N is a nucleic acid sequence composed of from about 0-25 nucleotides.

49. (Twice Amended) The method of claim 42, wherein the CpG oligonucleotide has a sequence including at least the following formula:

5' $TCNTX_1X_2CGX_3X_4$ 3' (SEQ ID NO:89)

wherein $X_1$, $X_2$, $X_3$, and $X_4$ are nucleotides, N is a nucleic acid sequence composed of from about 0-25 nucleotides.

62. (Twice Amended) The method of claim 51, wherein the CpG oligonucleotide has a sequence including at least the following formula:

5' $TCNTX_1X_2CGX_3X_4$ 3' (SEQ ID NO:89)

wherein $X_1$, $X_2$, $X_3$, and $X_4$ are nucleotides, N is a nucleic acid sequence composed of from about 0-25 nucleotides.

68. (Amended) The method of claim 66, wherein the CpG oligonucleotide has a sequence including at least the following formula:

5' $TCNTX_1X_2CGX_3X_4$ 3' (SEQ ID NO:89)

wherein $X_1$, $X_2$, $X_3$, and $X_4$ are nucleotides, N is a nucleic acid sequence composed of from about 0-25 nucleotides.

Respectfully submitted,

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**X: October 12, 2001**